



01-27-04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Ilan et al

Serial No. 10/676,045

Group Art Unit: Not yet determined

Filed: September 30, 2003

Examiner: Not yet determined

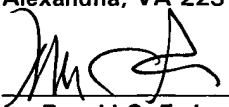
Title: EDUCATED NKT CELLS AND THEIR USES IN THE TREATMENT OF IMMUNE-RELATED DISORDERS

TRANSMITTAL  
INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an Information Disclosure Statement which is being filed in accordance with 37 C.F.R. §§ 1.56 and 1.97-1.98. The items listed on Form PTO-1449, a copy of which is enclosed, may be deemed to be pertinent to the above-identified application and are made of record to assist the Patent and Trademark Office in its examination of this application. The Examiner is respectfully requested to fully consider the items and to independently ascertain their teaching.

EXPRESS MAIL CERTIFICATE	
"Express Mail" Label No.:	<u>EL701001103US</u>
Deposit Date:	<u>January 26, 2004</u>
I hereby certify that this paper and the attachments herein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.110 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.	
 Ronald C. Fedus Reg. No. 32,567	<u>JAN 26 2004</u> Date

01/29/2004 WABDELRI 00000146 051135 10676045

01 FC:1460 130.00 DA

Enz-63(CIP)



- [ ] For each of the following items listed on the enclosed copy of Form PTO-1449 that is not in the English language, an English language translation of that item or a portion thereof or a concise explanation of the relevance of that item is enclosed:
2. [ ] For each of the following items listed on the enclosed copy of form PTO-1449 that is not in the English language, a concise explanation of the relevance of that item is incorporated in the specification of the above-identified application.
3. [ ] Any copy of the items on the enclosed copy of Form PTO-1449 that is not enclosed with this Information Disclosure Statement was previously cited by or submitted to the Patent and Trademark Office in the prior [ ] Divisional or [ ] Continuation-In-Part application under 37 C.F.R. §1.60, U.S. Serial No. \_\_\_\_\_, filed \_\_\_\_\_.
4. [ ] No fee is due under 37 C.F.R. §1.17(p) for this Information Disclosure Statement since it is being filed in compliance with:
- [ ] 37 C.F.R. §1.97(b)(1), within three months of the filing date of the above-identified application.
  - [ ] 37 C.F.R. §1.97(b)(2), within three months of the date of entry into the national stage as set forth in §1.491 in an international application.
  - [ ] 37 C.F.R. §1.97(b)(3), before the mailing date of a first Office action on the merits.
5. [ ] No fee is due under 37 C.F.R. §1.17(p) for this Information Disclosure Statement since it is being filed in compliance with 37 C.F.R. §1.97(c), after the period specified in paragraph 4 above but before the mailing date of a final action or a Notice of Allowance (where there has been no prior final action), and is accompanied by one of the certifications pursuant to 37 C.F.R. §1.97(e) set forth in paragraph 9 below.
6. [x] A fee is due under 37 C.F.R. §1.17(p) for this Information Disclosure Statement since it is being filed in compliance with 37 C.F.R. §1.97(c), after the period specified in paragraph 4 above but before the mailing date of a final action or a notice of allowance (where there has been no prior final action):
- [ ] A check in the amount of \$180.00 is enclosed in payment of the fee.

Enz-63(CIP)

[x] Charge the fee to Deposit Account No. 05-1135, Order No. **Enz-63(CIP)**. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

7. [ ] A fee is due under 37 C.F.R. §1.17(i)(1) for this Information Disclosure Statement since it is being filed in compliance with 37 C.F.R. §1.97(d), after the mailing date of a final action or a notice of allowance, whichever comes first, but before payment of the issue fee, and is accompanied by:
- a. one of the certification pursuant to 37 C.F.R. §1.97(e) set forth in paragraph 9 below; and
  - b. the attached petition requesting consideration of this Information Disclosure Statement; and
  - c. the fee due under 37 C.F.R. §1.17(i)(1) which is paid as set forth in paragraph 10 below.
8. [ ] A fee is due under 37 C.F.R. §1.17(i)(1) for this Information Disclosure Statement since it is being filed in compliance with:
- a. [ ] 37 C.F.R. §1.313(b)(3), after the issue fee has been paid and information cited in this Information Disclosure Statement may render at least one claim unpatentable and is accompanied by the attached Petition To Withdraw Application From Issue;
  - b. [ ] 37 C.F.R. §1.313(b)(5), after the issue fee has been paid and information cited in this Information Disclosure Statement is to be considered in a Continuation application upon abandonment of the instant application and is accompanied by the attached Petition To Withdraw Application From Issue.
  - c. [ ] The fee due under 37 C.F.R. §1.17(i)(1) is paid as set forth in paragraph 10 below.
9. [ ] I hereby certify that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement.
- [ ] I hereby certify that no item of information in the Information Disclosure Statement filed herewith was cited in a communication from a foreign patent office in a counterpart foreign application or, to my knowledge after making reasonable inquiry, was known to any individual designated in §1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

**Enz-63(CIP)**

10. [ ] A check in the amount of \$180.00 is enclosed in payment of the fee due under 37 C.F.R. §1.17(i)(1).


[X] Charge the fee under 37 C.F.R. §1.17(i)(1) to Deposit Account No. 05-1135. Order No. **Enz-63(CIP)**. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

[x] The Commissioner is hereby authorized to charge any additional fees which may be required for this Information Disclosure Statement, or credit any overpayment to Deposit Account No. 05-1135. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

Dated: January 26, 2004

By:



Ronald C. Fedus

Registration No. 32,567

Natalie Bogdanos

Registration No. 51,480

Attorneys for Applicants

Mailing Address:

ENZO LIFE SCIENCES, INC.  
c/o Enzo Biochem, Inc.  
292 Madison Avenue, 9<sup>th</sup> Floor  
New York, New York 10022  
Telephone: (212) 583-0100  
Telefax: (212) 583-0150

**Enz-63(CIP)**



Enz-63(CIP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Ilan et al

Serial No. 10/676,045

Filed: September 30, 2003

Title: EDUCATED NKT CELLS AND THEIR USES  
IN THE TREATMENT OF IMMUNE-RELATED  
DISORDERS

Group Art Unit: Not yet known

Examiner: Not yet known

527 Madison Avenue, 9<sup>th</sup> Floor  
New York, New York 10022  
January 26, 2004

**FILED VIA EXPRESS MAIL**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 C.F.R. §§1.56 & 1.971.98**

Dear Sirs:

Pursuant to the provisions of 37 C.F.R. §1.971.98, and in full compliance with their duty of disclosure under 37 C.F.R. §1.56, Applicants, through their attorney, are bringing the following one-hundred-thirty (130) documents to the attention of the U.S. Patent and Trademark Office and the Examiner handling their above-identified application:

Enz-63(CIP)

Ilan et al

Serial No.: 10/676,045

Filed: September 30, 2003

Page 2 [Information Disclosure Statement

- January 26, 2004]

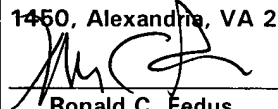
---

**EXPRESS MAIL CERTIFICATE**

"Express Mail" Label No.: EL701001103US

Deposit Date: January 26, 2004

I hereby certify that this paper and the attachments herein are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.110 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

  
Ronald C. Fedus

Reg. No. 32,567

JAN 26 2004  
Date

1. Adorini, L., et al., "Pathogenesis and immunotherapy of autoimmune diseases," Immunol. Today 18:209-211 (1997) [Exhibit 1];
2. Arase, H., et al., "NK1.1 + CD4 + CD8- thymocytes with specific lymphokine secretion," Eur. J. Immunol. 23:307-310 (1993) [Exhibit 2];
3. Arase, H., et al., "Interferon gamma production by natural killer (NK) cells and NK1.1 + T cells upon NKR-P1 cross-linking," J. Exp. Med. 183:2391-2396 (1996) [Exhibit 3];
4. Arase, H., et al., "Lymphokine-activated killer cell activity of CD4-CD8- TCR alpha beta + thymocytes," J. Immunol. 151:546 (1993) [Exhibit 4];
5. Ballas, Z.K., et al., "Lymphokine-activated killer cells. VII. IL-4 induces an NK1.1 + CD8 alpha + beta- TCR-alpha beta B220 + lymphokine-activated killer subset," J. Immunol. 150:17-30 (1993) [Exhibit 5];
6. Bendelac, A., et al., "MOUSE CD1-SPECIFIC NK1 T CELLS: Development, Specificity, and Function," Annu. Rev. Immunol. 15:535-562 (1997) [Exhibit 6];
7. Bendelac, A., et al., "Mouse NK1 + T cells," Curr. Opin. in Immunol. 7:367-374 (1995) [Exhibit 7];
8. Blanas, E., et al., "Induction of Autoimmune Diabetes by Oral Administration of Autoantigen," Science 274:1707-1709 (1996) [Exhibit 8];
9. Bleicher, P.A., et al., "Expression of murine CD1 on gastrointestinal epithelium," Science 250:679-682 (1990) [Exhibit 9];
10. Callery, M.P., et al., "The effect of portacaval shunt on delayed-hypersensitivity responses following antigen feeding," J. Surg. Res. 46:391-394 (1989) [Exhibit 10];
11. Carvalho, C.R., et al., "Indirect effects of oral tolerance cannot be ascribed to bystander suppression," Scand. J. Immunol. 45:276-281 (1997) [Exhibit 11];
12. Chen, H., et al., "Cultured NK1.1 + CD4 + T cells produce large amounts of IL-4 and IFN- gamma upon activation by anti-CD3 or CD1," J. Immunol. 159:2240-2249 (1997) [Exhibit 12];

13. Chiba, M., et al., "Human colonic intraepithelial and lamina proprial lymphocytes: cytotoxicity in vitro and the potential effects of the isolation method on their functional properties," Gut 22:177-182 (1981) [Exhibit 13];
14. Coligan, J.E., et al., *Current Protocols in Immunology*, Wiley and Sons (1994) [Exhibit 14];
15. Collins, C., et al., "RAG1, RAG2 and pre-T cell receptor alpha chain expression by adult human hepatic T cells: evidence for extrathymic T cell maturation," Eur. J. Immunol. 26:3114-3118 (1996) [Exhibit 15];
16. Crispe, I.N., et al., "Strange brew: T cells in the liver," Immun. Today 17:522-525 (1996) [Exhibit 16];
17. Crispe, I.N., et al., "The liver as a site of T-cell apoptosis: graveyard, or killing field?," Immunol. Review 174:47-62 (2000) [Exhibit 17];
18. Cui, J., et al., "Inhibition of T Helper Cell Type 2 Cell Differentiation and Immunoglobulin E Response by Ligand-activated V $\alpha$ 14 Natural Killer T Cells," J. Exp. Med. 190(6):783-792 (1999) [Exhibit 18];
19. Das, K.M., et al., "A shared and unique epitope(s) on human colon, skin and biliary epithelium detected by a monoclonal antibody," Gastroenterology 98:464-69 (1990) [Exhibit 19];
20. Dasgupta, A., et al., "Circulating immunoglobulin G1 in patients with ulcerative colitis against the colonic epithelial protein detected by a novel monoclonal antibody," Gut 35:1712-1717 (1994) [Exhibit 20];
21. David, G.S., et al., United States Patent No. 4,376,110, filed August 4, 1980 [Exhibit 21];
22. Doherty, D.G., et al., "Distinct cytotoxic lymphocytes subsets suggest a role for the liver in immune homeostasis," J. Hepatology 28:59 (1998) [Exhibit 22];
23. Doherty, D.G., et al., "Human lymphocytes with dual T cell and natural killer cell phenotype and function in the normal adult liver," Hepatology 26:445A (1997) [Exhibit 23];

24. Garcia-Barcina, M., et al., "Detection of cell-adhesion molecules on human liver-associated lymphocytes," Immunol. 82:95-98 (1994) [Exhibit 24];
25. Hancock, W., et al., "Suppression of Insulinitis in Non-Obese Diabetic (NOD) Mice by Oral Insulin Administration Is Associated with Selective Expression of Interleukin-4 and -10, Transforming Growth Factor- $\beta$ , and Prostaglandin-E," Am. J. Path. 147(5):1193-1197 (1995) [Exhibit 25];
26. Hashimoto, W., et al., "Cytotoxic NK1.1 Ag + alpha beta T cells with intermediate TCR induced in the liver of mice by IL-12," J. Immunol. 154:4333-4340 (1995) [Exhibit 26];
27. Hayakawa, T., et al., "Murine thymic CD4 + T cell subsets: a subset (Thy0) that secretes diverse cytokines and overexpresses the V beta 8 T cell receptor gene family," J. Exp. Med. 176:269-274 (1992) [Exhibit 27];
28. Hibi, S., et al., "Circulating antibodies to the surface antigens on colon epithelial cells in ulcerative colitis," Clin. Exp. Immunol. 54:163-168 (1983) [Exhibit 28];
29. Ilan, Y., et al., "Treatment of experimental colitis through induction of oral tolerance towards colitis-extracted proteins," Gastro 114:260 (1998) [Exhibit 29];
30. Jonsson, J.R., et al., "Expression of FAS/FASL and BCL-2 in normal human liver derived leucocytes," Hepatology 26:269A (1997) [Exhibit 30];
31. Kawamura, T., et al., "Cutting Edge: Critical Role of NK1 + T Cells in IL-12-Induced Immune Responses In Vivo," J. Immunol. 160:16-19 (1998) [Exhibit 31];
32. Kitamura, H., et al., "The Natural Killer T (NKT) Cell Ligand  $\alpha$  Galactosylceramide Demonstrates Its Immunopotentiating Effect by Inducing Interleukin (IL)-12 Production by Dendritic Cells and IL-12 Receptor Expression on NKT Cells," J. Exp. Med. 189:1121-1127 (1999) [Exhibit 32];
33. Kohler, G., et al., "Continuous cultures of fused cells secreting antibody of predefined specificity," Nature 256:495-497 (1975) [Exhibit 33];
34. Kuhn, R., et al., "Interleukin-10-deficient mice develop chronic enterocolitis," Cell 75:263-274 (1993) [Exhibit 34];

35. Leite-De-Moraes, M.C., et al., "IL-4-producing NK T cells are biased towards IFN-gamma production by IL-12. Influence of the microenvironment on the functional capacities of NK T cells," Eur. J. Immunol. **28**:1507-1515 (1998) [Exhibit 35];
36. Ma, X., et al., "The interleukin 12 p40 gene promoter is primed by interferon gamma in monocytic cells," J. Exp. Med. **183**:147-157 (1996) [Exhibit 36];
37. Mabuchi, A., et al., "Role of the liver in T cell differentiation--generation of CD3-CD4 + /CD8 + TCRbeta- cells and CD3-4-8-TCRbeta + cells from CD4-8-TCRbeta- athymic nude bone marrow cells by culture with parenchymal liver cells," J. Leukocyte Biology **63**:575-583 (1998) [Exhibit 37];
38. MacDonald, R.H., "NK1.1 + T cell receptor-alpha/beta + cells: new clues to their origin, specificity, and function," J. Exp. Med. **182**:633-638 (1995) [Exhibit 38];
39. Madsen, K.L., et al., "Interleukin 10 prevents cytokine-induced disruption of T84 barrier integrity and limits chloride secretion," Gastroenterology **113**:151-159 (1997) [Exhibit 39];
40. Marth, T., et al., "High dose oral tolerance in ovalbumin TCR-transgenic mice: systemic neutralization of IL-12 augments TGF-beta secretion and T cell apoptosis," J. Immunol. **157**:2348-2357 (1996) [Exhibit 40];
41. Matzinger, P., "Tolerance, danger, and the extended family," Ann. Rev. Immunol. **12**:991-1045 (1994) [Exhibit 41];
42. Mizoguchi, A., et al., "Cytokine imbalance and autoantibody production in T cell receptor-alpha mutant mice with inflammatory bowel disease," J. Exp. Med. **183**:847-856 (1996) [Exhibit 42];
43. Murch, S.H., et al., "Location of tumour necrosis factor alpha by immunohistochemistry in chronic inflammatory bowel disease," Gut **34**:1705 (1998) [Exhibit 43];
44. Nakano, Y., et al., "Permanent acceptance of liver allografts by intraportal injection of donor spleen cells in rats," Surgery **111**:668-676 (1992) [Exhibit 44];

45. Neurath, M.F., et al., "Antibodies to interleukin 12 abrogate established experimental colitis in mice," J. Exp. Med. 182:1281-1290 (1995) [Exhibit 45];
46. Neurath, M., et al., "Experimental granulomatous colitis in mice is abrogated by induction of TGF-beta-mediated oral tolerance," J. Exp. Med. 183:2605-2616 (1996) [Exhibit 46];
47. Onoe, Y., et al., "Involvement of both donor cytotoxic T lymphocytes and host NK1.1 + T cells in the thymic atrophy of mice suffering from acute graft-versus-host disease," Immunology 95:248-256 (1998) [Exhibit 47];
48. Parronchi, P., et al., "Type 1 T-helper cell predominance and interleukin-12 expression in the gut of patients with Crohn's disease," Am. J. Pathol. 150:823-832 (1997) [Exhibit 48];
49. Podolsky, D.K., et al., "Inflammatory bowel disease," New Engl. J. Med. 325:928-935 (1991) [Exhibit 49];
50. Pouwels, P.H., et al., *Cloning Vectors, A Laboratory Manual*, Elsevier, New York (1985) [Exhibit 50];
51. Powrie, F., et al., "Inhibition of Th1 responses prevents inflammatory bowel disease in scid mice reconstituted with CD45RBhi CD4 + T cells," Immunity 1:553-562 (1994) [Exhibit 51];
52. Qin, S., et al., "'Infectious' Transplantation Tolerance," Science 259:974-977 (1993) [Exhibit 52];
53. Rabbani, E., et al., European Patent Application No. 1 149 586 A1, filed April 27, 2001 [Exhibit 53];
54. Raedler, A., et al., "Elevated numbers of peripheral T cells in inflammatory bowel diseases displaying T9 antigen and Fc alpha receptors," Clin. Exp. Immunol. 60:518-526 (1985) [Exhibit 54];
55. Rodriguez, R.L., et al., *Vectors: A Survey of Molecular Cloning Vectors and their Uses*, Butterworth-Heinemann, Boston (1987) [Exhibit 55];

56. Roy-Chowdhury, et al., International Patent Application No. WO 98/37917, filed February 26, 1998, continuing U.S. application subsequently published as 2003-0170258, published on September 11, 2003; U.S. publication provided herein as reference [Exhibit 56];
57. Sadlack, B., et al., "Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene," Cell 75:253-261 (1993) [Exhibit 57];
58. Sander, J.H., et al., "Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's Disease Study Group," Gastroenterology 113:383-89 (1997) [Exhibit 58];
59. Seder, R.A., et al., "Acquisition of Lymphokine-Producing Phenotype by CD4 + T Cells," Annu. Rev. Immuno. 12:635-673 (1994) [Exhibit 59];
60. Seder, R.A., et al., "Interleukin 12 Acts Directly on CD4 + T Cells to Enhance Priming for Interferon  $\gamma$  Production and Diminishes Interleukin 4 Inhibition of Such Priming," Proc. Natl. Acad. Sci. USA 90:10188-10192 (1993) [Exhibit 60];
61. Seki, S., et al., "Unusual alpha beta-T cells expanded in autoimmune lpr mice are probably a counterpart of normal T cells in the liver," J. Immunol. 147:1214-1221 (1991) [Exhibit 61];
62. Sellon, R.K., et al., "Resident Enteric Bacteria are Necessary for Development of Spontaneous Colitis and Immune System Activation in Interleukin-10-Deficient Mice," Infection and Immunity 66:5224-5231 (1998) [Exhibit 62];
63. Strober, W., et al., "Reciprocal IFN-gamma and TGF-beta responses regulate the occurrence of mucosal inflammation," Immunol. Today 18:61-64 (1997) [Exhibit 63];
64. Strober, W., et al., *In Clinical Immunology*, Mosby, St. Louis, pp. 1401-1428 (1995) [Exhibit 64];
65. Takahashi, F., et al., "Isolation and characterization of a colonic autoantigen specifically recognized by colon tissue-bound immunoglobulin G from idiopathic ulcerative colitis," J. Clin. Invest. 76:311-318 (1985) [Exhibit 65];

66. Takahashi, M., et al., "LPS induces NK1.1 + alpha beta T cells with potent cytotoxicity in the liver of mice via production of IL-12 from Kupffer cells," J. Immunol. 156:2436-2442 (1996) [Exhibit 66];
67. Telemo, E., et al., "Oral tolerance in experimental animals," Int. Arch. Allergy Immunol. 113:219-223 (1997) [Exhibit 67];
68. Trop, S., et al., "Liver-Associated Lymphocytes Expressing NK1.1 Are Essential for Oral Immune Tolerance Induction in a Murine Model," Hepatology 29:746-755 (1999) [Exhibit 68];
69. Vicari, A.P., et al., "Mouse NK1.1 + T cells: a new family of T cells," Immunology Today 17(2):71 (1996) [Exhibit 69];
70. Von Herrath, M.G., et al., "Oral Insulin Treatment Suppresses Virus-induced Antigen-specific Destruction of  $\beta$  Cells and Prevents Autoimmune Diabetes in Transgenic Mice," J. Clin. Invest. 98:1324-1331 (1996) [Exhibit 70];
71. Wahl, et al., "Improved radioimaging and tumor localization with monoclonal F(ab')<sub>2</sub>," J. Nucl. Med. 24:316-325 (1983) [Exhibit 71];
72. Weiner, H., et al., "Oral Tolerance: Immunologic Mechanisms and Treatment of Animal and Human Organ-Specific Autoimmune Diseases by Oral Administration of Autoantigens," Annu. Rev. Immunol. 12:809-837 (1994) [Exhibit 72];
73. Weiner, H., et al., "Oral Tolerance," Proc. Natl. Acad. Sci. USA 91:10762-10765 (1994) [Exhibit 73];
74. Weiner, H.L., et al., "Oral tolerance: immune mechanisms and treatment of autoimmune diseases," Immunol. Today 18:335-343 (1997) [Exhibit 74];
75. Weiner, H.L., et al., "Double-blind pilot trial of oral tolerization with myelin antigens in multiple sclerosis," Science 259:1321-1324 (1993) [Exhibit 75];
76. Yoshimoto, T., et al., "CD4pos, NK1.1pos T cells promptly produce interleukin 4 in response to in vivo challenge with anti-CD3," J. Exp. Med. 179:1285-1295 (1994) [Exhibit 76];
77. Yoshimoto, T., et al., "Role of NK1.1 + T Cells in a TH2 Response and in Immunoglobulin E Production," Science 270:1845-1847 (1995) [Exhibit 77];

78. Yu, S.Y., et al., "Portal vein administration of donor cells promotes peripheral allospecific hyporesponsiveness and graft tolerance," Surgery 116:229-234 (1994) [Exhibit 78];
79. Angulo, P., "Nonalcoholic fatty liver disease," New England J. of Medicine 346:1221-1231 (2002) [Exhibit 79];
80. Caldwell, S.H., et al., "Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease," Hepatology 29:664-669 (1999) [Exhibit 80];
81. Chandra, R.K., et al., "Immunocompetence in obesity," Acta Paediatr. Scand. 69:25-30 (1980) [Exhibit 81];
82. Cohen, B., et al., "Modulation of Insulin Activities by Leptin," Science 274:1185 (1996) [Exhibit 82];
83. Cortez-Pinto, H., et al., "Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study," JAMA 282:1659-1664 (1999) [Exhibit 83];
84. Diehl, A.M., et al., "Nonalcoholic Steatosis and Steatohepatitis IV. Nonalcoholic fatty liver disease abnormalities in macrophage function and cytokines," J. Physiol. Gastrointest. Liver Physiol 282:G1-G5 (2002) [Exhibit 84];
85. Faggioni, R., et al., "Leptin-deficient (*ob/ob*) mice are protected from T cell-mediated hepatotoxicity: Role of tumor necrosis factor  $\alpha$  and IL-18," Proc. Natl. Acad. Sci. USA 97:2367-2372 (2000) [Exhibit 85];
86. Feingold, C.T., et al., "Role of cytokines in inducing hyperlipidemia," Diabetes 41(Suppl 2):97-101 (1992) [Exhibit 86];
87. Ferrara, J.L.M., et al., "Graft-versus-host disease," New Eng. J. of Med. 324:667-672 (1991) [Exhibit 87];
88. Field, C.J., et al., "Changes in circulating leukocytes and mitogen responses during very-low- energy all-protein reducing diets," Am. J. Clin. Nutr. 54:123-129 (1991) [Exhibit 88];

89. George, D.K., et al., "Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis," Gastroenterology **114**:311-318 (1998) [Exhibit 89];
90. Godfrey, D.J., et al., "NKT cells: Facts, functions and fallacies," Immunol. Today **21**:573-583 (2000) [Exhibit 90];
91. Harrison, S.A., et al., "Vitamin E and Vitamin C in the Treatment of Nonalcoholic Steatohepatitis. A Prospective, Randomized, Placebo-Controlled Clinical Trial. A Preliminary Report," Gastroenterology **123**:M1332 (2002) [Exhibit 91];
92. Hotamisligil, G.S., et al., "Adipose expression of tumor necrosis factor-[alpha]: direct role in obesity-linked insulin resistance," Science **259**:87-91 (1993) [Exhibit 92];
93. Hotamisligil, G.S., "The role of TNFalpha and TNF receptors in obesity and insulin resistance," J. Internal Med. **245**:621-625 (1999) [Exhibit 93];
94. Howard, J.K., et al., "Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in *ob/ob* mice," J. Clin. Invest. **104**:1051-1059 (1999) [Exhibit 94];
95. Hruszkewycz, A.M., et al., "Evidence for mitochondrial DNA damage by lipid peroxidation," Biochem. Biophys. Res. Commun. **153**:191-197 (1988) [Exhibit 95];
96. Ilan, Y., et al., U.S. Patent Application No. 10/451,811 filed June 25, 2003, a 371 of International Patent Application No. PCT/IL01/01197, subsequently published as WO 02/051986 on July 4, 2002; published version provided herein [Exhibit 96];
97. Koffler, M., et al., "Immunobiological consequence of regulation of insulin receptor on alloactivated lymphocytes in normal and obese subjects," Diabetes **40**:364-370 (1991) [Exhibit 97];
98. Krishnan, E., et al., "Study of function and maturation of monocytes in morbidly obese individuals," J. Surg. Res. **33**:89-97 (1982) [Exhibit 98];

99. Li, Z., et al., "Murine leptin deficiency alters Kupffer cell production of cytokines that regulate the innate immune system," Gastroenterology 123:1304-1310 (2002) [Exhibit 99];
100. Loffreda, S., et al., "Leptin regulates proinflammatory immune responses," FASEB J 12:57-67 (1998) [Exhibit 100];
101. Lord, G.M., et al., "Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression," Nature 394:897-901 (1998) [Exhibit 101];
102. Mattacks, C.A., et al., "Interactions of noradrenalin and tumour necrosis factor alpha, interleukin 4 and interleukin 6 in the control of lipolysis from adipocytes around lymph nodes," Cytokine 11:334-346 (1999) [Exhibit 102];
103. Matteoni, C.A., et al., "Nonalcoholic Fatty Liver Disease: A Spectrum of Clinical and Pathological Severity," Gastroenterology 116:1413 (1999) [Exhibit 103];
104. Mitchell, D.G., et al., "Chemical shift phase-difference and suppression magnetic resonance imaging techniques in animals, phantoms and humans: fatty liver," Invest. Radiol. 26:1041-1052 (1991) [Exhibit 104];
105. Montague, C.T., et al., "Depot-related gene expression in human subcutaneous and omental adipocytes," Diabetes 47:1384-1391 (1998) [Exhibit 105];
106. Nagler, A., et al., "Induction of oral tolerance in bone marrow transplantation recipients suppresses graft-versus-host disease in a semiallogeneic mouse model," Bone Marrow Transplantation 32:363-369 (2003) [Exhibit 106];
107. Ogawa, H., et al., "Cachectin/tumor necrosis factor and interleukin-1 show different modes of combined effect on lipoprotein lipase activity and intracellular lipolysis in 3T3-L1 cells," Biochimica et Biophysica Acta 1003:131-135 (1989) [Exhibit 107];
108. Pellymouter, M.A., et al., "Effects of the obese gene product on body weight regulation in ob/ob mice," Science 269:540-543 (1995) [Exhibit 108];

109. Pond, C.M., et al., "Long-term changes in adipose tissue in human disease," Proc. Nutr. Soc. 60:365-374 (2001) [Exhibit 109];
110. Purohit, A., et al., "Aromatase activity and interleukin-6 production by normal and malignant breast tissues," J. Clin. Endocr. & Metab. 80:3052-3058 (1995) [Exhibit 110];
111. Rosen, B.S., et al., "Adipsin and complement factor D activity: an immune-related defect in obesity," Science 244:1483-1487 (1989) [Exhibit 111];
112. Roy-Chowdhury, et al., U.S. Patent Application No. 08/808,629 filed February 28, 1997, with continuing applications No. 10/377,628 filed March 4, 2003 and 10/377,603 filed March 4, 2003, and divisional application no. 09/447,704 filed November 23, 1998, provided herein as reference [Exhibit 112];
113. Sanyal, A.J., et al., "Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities," Gastroenterology 120:1183-1192 (2001) [Exhibit 113];
114. Sarraf, P., et al., "Multiple Cytokines and Acute Inflammation Raise Mouse Leptin Levels: Potential Role in Inflammatory Anorexia," J. Exp. Med. 185:171-175 (1997) [Exhibit 114];
115. Shilobet, O., et al., "NKT and CD8 lymphocytes mediate suppression of hepatocellular carcinoma growth via tumor antigen-pulsed dendritic cells," Int. J. Cancer 106:236-243 (2003) [Exhibit 115];
116. Taylor, P.A., et al., "The infusion of ex vivo activated and expanded CD4<sup>+</sup>CD25<sup>+</sup> immune regulatory cells inhibits graft-versus-host disease lethality," Blood 99:3493-3499 (2002) [Exhibit 116];
117. Tomohiro, N., et al., "Adrenal Masses: Quantification of Fat Content with MR Images," Radiology 218:642-646 (2001) [Exhibit 117];
118. Trop, S., et al., "NK 1.1 + T Cell: A Two-Faced Lymphocyte in Immune Modulation of the IL-4/IFN- Paradigm," J. Clin. Immunol. 22:270-280 (2002) [Exhibit 118];

119. Uysal, K.T., et al., "Protection from obesity-induced insulin resistance in mice lacking Tnf- $\alpha$  function," Nature 389:610-614 (1997) [Exhibit 119];
120. Vogelsang, G.B., et al., "Graft versus host disease: Implications from basic immunology for prophylaxis and treatment," Cancer Treat. Res. 77:87-97 (1997) [Exhibit 120];
121. Yang, et al., "Obesity increases sensitivity to endotoxin liver injury: Implications for the pathogenesis of steatohepatitis," Proc. Natl. Acad. Sci USA 94:2557-2562 (1997) [Exhibit 121];
122. Zeng, D., et al., "Bone Marrow NK1.1<sup>+</sup> and NK1.1<sup>+</sup> T Cells Reciprocally Regulate Acute Graft versus Host Disease," J. Exp. Med. 189:1073-1081 (1999) [Exhibit 122];
123. Zhang, Y., et al., "Positional cloning of the mouse obese gene and its human homologue," Nature 372:425-432 (1994) [Exhibit 123];
124. Burdin, N., et al., "Immunization with alpha-galactosylceramide polarizes CD1-reactive NK T cells towards Th2 cytokine synthesis," Eur J. Immunol. 29:2014-2025 (1999) [Exhibit 10];
125. Gotsman, I., et al., "Effect of peripheral immune tolerance on liver-associated lymphocytes expressing NK1.1," Transplant Proc. 32:749-750 (2000) [Exhibit 125];
126. Levinson, D.A., U.S. Patent No. 5,721,351, filed June 7, 1995 [Exhibit 126];
127. Levinson, D.A., U.S. Patent No. 6,066,498, filed June 7, 1995 [Exhibit 127];
128. Levinson, D.A., U.S. Patent No. 6,066,322, filed March 3, 1995 [Exhibit 128];
129. Shlomai, A., et al., "Immunomodulation of experimental colitis: the role of NK1.1 liver lymphocytes and surrogate antigens – bystander effect," J. Pathology 195:498-507 (2001) [Exhibit 129];

130. Sredni, B., et al., "Predominance of TH1 response in tumor-bearing mice and cancer patients treated with AS101," J. Natl. Cancer Inst. 88:1276-1284 (1996) [Exhibit 130];

The first one-hundred-twenty-three (123) foregoing references (numbers 1-123) were cited in the specification of the instant application.

The seven (7) subsequent references (numbers 124-130) were cited in the International Search Report dated May 22, 2002 of the parent PCT Application (Publication No. WO 02/051986, published July 4, 2002).

A completed Form PTO-1449 listing the 130 above-submitted documents is also attached hereto as Exhibit 131.

By this voluntary citation of art, Applicants and their attorney are requesting that the documents be made of record in the present application.

The above citation of documents is not a representation that these documents constitute a complete or exhaustive listing, nor that the above listing necessarily includes the closest or most relevant documents, nor are these documents necessarily a complete listing of all documents known to Applicants or their attorney. It is simply a voluntary citation of documents made in good faith, which is not intended to serve in any way as a substitute for the Examiner's own search.

In view of the general and specific features described and claimed in the present application, Applicants respectfully submit that the present invention is neither disclosed nor suggested by the documents referred to above and is thus patentably distinct thereover. Furthermore, Applicants do not believe, and do not submit, by the citation of these references, that these documents, either by themselves or in combination with other documents, render the invention *prima facie* obvious under the duty of disclosure rules.

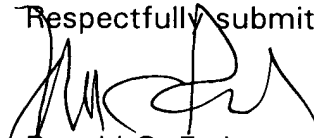
Applicants respectfully request that the Examiner make the above-submitted documents of record in the instant application. Applicants further request that the

Ilan et al  
Serial No.: 10/676,045  
Filed: September 30, 2003  
Page 16 [Information Disclosure Statement  
– January 26, 2004]

Examiner consider these documents as any of them may relate to the instant application.

The fee under 37 C.F.R. §1.17(p) for filing this Information Disclosure Statement is \$180.00. The Patent and Trademark Office is hereby authorized to charge the amount of this fee (and any other fees in connection with this IDS) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

Respectfully submitted,



Ronald C. Fedus  
Registration No. 32,567  
Natalie Bogdanos  
Registration No. 51,480  
Attorneys for Applicants

ENZO LIFE SCIENCES, INC.  
c/o Enzo Biochem, Inc.  
527 Madison Avenue, 9<sup>th</sup> Floor  
New York, New York 10022  
Tel. (212) 583-0100

Form PTO-1449 U.S. Department of Commerce

(REV. 8-83) Patent and Trademark Office

## INFORMATION DISCLOSURE CITATION

(use several sheets if necessary)

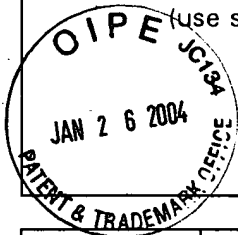
Atty. Docket No.  
ENZ-63(CIP)

Serial No. 10/676,045

Applicants: Ilan, et al

Filed: Sep. 30, 2003

Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE
	4 3 7 6 1 1 0		David, et al.			
	0 1 7 0 2 5 8	2003	Roy-Chowdhury, et al.			
	5 7 2 1 3 5 1		Levinson			
	6 0 6 6 4 9 8		Levinson			
	6 0 6 6 3 2 2		Levinson			

## FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRANS- LATION YES NO
EP	1 1 4 9 5 8 6		Rabbani, et al	A1		
WO	0 5 1 9 8 6	2002	Ilan, et al			

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

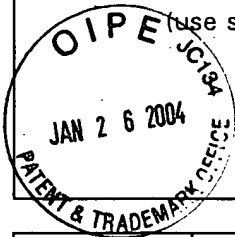
	Adorini, L., et al., "Pathogenesis and immunotherapy of autoimmune diseases," <u>Immunol. Today</u> 18:209-211 (1997)
	Arase, H., et al., "NK1.1 + CD4+ CD8- thymocytes with specific lymphokine secretion," <u>Eur. J. Immunol.</u> 23:307-310 (1993)
	Arase, H., et al., "Interferon gamma production by natural killer (NK) cells and NK1.1 + T cells upon NKR-P1 cross-linking," <u>J. Exp. Med.</u> 183:2391-2396 (1996)
	Arase, H., et al., "Lymphokine-activated killer cell activity of CD4-CD8- TCR alpha beta + thymocytes," <u>J. Immunol.</u> 151:546 (1993)
	Ballas, Z.K., et al., "Lymphokine-activated killer cells. VII. IL-4 induces an NK1.1 + CD8 alpha + beta- TCR-alpha beta B220 + lymphokine-activated killer subset," <u>J. Immunol.</u> 150:17-30 (1993)
	Bendelac, A., et al., "MOUSE CD1-SPECIFIC NK1 T CELLS: Development, Specificity, and Function," <u>Annu. Rev. Immunol.</u> 15:535-562 (1997)
	Bendelac, A., et al., "Mouse NK1 + T cells," <u>Curr. Opin. in Immunol.</u> 7:367-374 (1995)
	Blanas, E., et al., "Induction of Autoimmune Diabetes by Oral Administration of Autoantigen," <u>Science</u> 274:1707-1709 (1996)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office INFORMATION DISCLOSURE CITATION (use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE
	09	4 4 7 7 0 4	1998	Roy-Chowdhury et al			

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Bleicher, P.A., et al., "Expression of murine CD1 on gastrointestinal epithelium," <u>Science</u> 250:679-682 (1990)
	Callery, M.P., et al., "The effect of portacaval shunt on delayed-hypersensitivity responses following antigen feeding," <u>J. Surg. Res.</u> 46:391-394 (1989)
	Carvalho, C.R., et al., "Indirect effects of oral tolerance cannot be ascribed to bystander suppression," <u>Scand. J. Immunol.</u> 45:276-281 (1997)
	Chen, H., et al., "Cultured NK1.1+ CD4+ T cells produce large amounts of IL-4 and IFN-gamma upon activation by anti-CD3 or CD1," <u>J. Immunol.</u> 159:2240-2249 (1997)
	Chiba, M., et al., "Human colonic intraepithelial and lamina propria lymphocytes: cytotoxicity in vitro and the potential effects of the isolation method on their functional properties," <u>Gut</u> 22:177-182 (1981)
	Coligan, J.E., et al., <i>Current Protocols in Immunology</i> , Wiley and Sons (1994)
	Collins, C., et al., "RAG1, RAG2 and pre-T cell receptor alpha chain expression by adult human hepatic T cells: evidence for extrathymic T cell maturation," <u>Eur. J. Immunol.</u> 26:3114-3118 (1996)
	Crispe, I.N., et al., "Strange brew: T cells in the liver," <u>Immun. Today</u> 17:522-525 (1996)
	Crispe, I.N., et al., "The liver as a site of T-cell apoptosis: graveyard, or killing field?," <u>Immunol. Review</u> 174:47-62 (2000)
	Cui, J., et al., "Inhibition of T Helper Cell Type 2 Cell Differentiation and Immunoglobulin E Response by Ligand-activated V $\alpha$ 14 Natural Killer T Cells," <u>J. Exp. Med.</u> 190(6):783-792 (1999)

EXAMINER	DATE CONSIDERED
*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Form PTO-1449 U.S. Department of Commerce

(REV. 8-83) Patent and Trademark Office

Atty. Docket No.  
ENZ-63(CIP)

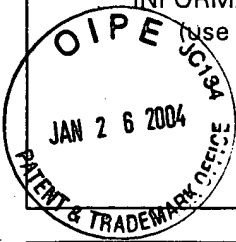
Serial No. 10/676,045

INFORMATION DISCLOSURE CITATION  
(use several sheets if necessary)

Applicants: Ilan, et al

Filed: Sep. 30, 2003

Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

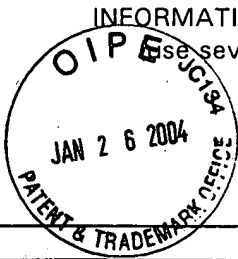
	Das, K.M., et al., "A shared and unique epitope(s) on human colon, skin and biliary epithelium detected by a monoclonal antibody," <u>Gastroenterology</u> 98:464-69 (1990)
	Dasgupta, A., et al., "Circulating immunoglobulin G1 in patients with ulcerative colitis against the colonic epithelial protein detected by a novel monoclonal antibody," <u>Gut</u> 35:1712-1717 (1994)
	Doherty, D.G., et al., "Distinct cytotoxic lymphocytes subsets suggest a role for the liver in immune homeostasis," <u>J. Hepatology</u> 28:59 (1998)
	Doherty, D.G., et al., "Human lymphocytes with dual T cell and natural killer cell phenotype and function in the normal adult liver," <u>Hepatology</u> 26:445A (1997)
	Garcia-Barcina, M., et al., "Detection of cell-adhesion molecules on human liver-associated lymphocytes," <u>Immunol.</u> 82:95-98 (1994)
	Hancock, W., et al., "Suppression of Insulinitis in Non-Obese Diabetic (NOD) Mice by Oral Insulin Administration Is Associated with Selective Expression of Interleukin-4 and -10, Transforming Growth Factor- $\beta$ , and Prostaglandin-E," <u>Am. J. Path.</u> 147(5):1193-1197 (1995)
	Hashimoto, W., et al., "Cytotoxic NK1.1 Ag + alpha beta T cells with intermediate TCR induced in the liver of mice by IL-12," <u>J. Immunol.</u> 154:4333-4340 (1995)
	Hayakawa, T., et al., "Murine thymic CD4 + T cell subsets: a subset (Thy0) that secretes diverse cytokines and overexpresses the V beta 8 T cell receptor gene family," <u>J. Exp. Med.</u> 176:269-274 (1992)
	Hibi, S., et al., "Circulating antibodies to the surface antigens on colon epithelial cells in ulcerative colitis," <u>Clin. Exp. Immunol.</u> 54:163-168 (1983)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

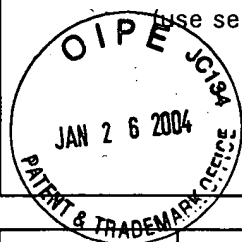
	Ilan, Y., et al., "Treatment of experimental colitis through induction of oral tolerance towards colitis-extracted proteins," <u>Gastro</u> 114:260 (1998)
	Jonsson, J.R., et al., "Expression of FAS/FASL and BCL-2 in normal human liver derived leucocytes," <u>Hepatology</u> 26:269A (1997)
	Kawamura, T., et al., "Cutting Edge: Critical Role of NK1 + T Cells in IL-12-Induced Immune Responses In Vivo," <u>J. Immunol.</u> 160:16-19 (1998)
	Kitamura, H., et al., "The Natural Killer T (NKT) Cell Ligand $\alpha$ Galactosylceramide Demonstrates Its Immunopotentiating Effect by Inducing Interleukin (IL)-12 Production by Dendritic Cells and IL-12 Receptor Expression on NKT Cells," <u>J. Exp. Med.</u> 189:1121-1127 (1999)
	Kohler, G., et al., "Continuous cultures of fused cells secreting antibody of predefined specificity," <u>Nature</u> 256:495-497 (1975)
	Kuhn, R., et al., "Interleukin-10-deficient mice develop chronic enterocolitis," <u>Cell</u> 75:263-274 (1993)
	Leite-De-Moraes, M.C., et al., "IL-4-producing NK T cells are biased towards IFN-gamma production by IL-12. Influence of the microenvironment on the functional capacities of NK T cells," <u>Eur. J. Immunol.</u> 28:1507-1515 (1998)
	Ma, X., et al., "The interleukin 12 p40 gene promoter is primed by interferon gamma in monocytic cells," <u>J. Exp. Med.</u> 183:147-157 (1996)
	Mabuchi, A., et al., "Role of the liver in T cell differentiation--generation of CD3-CD4 + /CD8 + TCRbeta- cells and CD3-4-8-TCRbeta + cells from CD4-8-TCRbeta-athymic nude bone marrow cells by culture with parenchymal liver cells," <u>J. Leukocyte Biology</u> 63:575-583 (1998)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office  INFORMATION DISCLOSURE CITATION (use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ian, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRANS- LATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	MacDonald, R.H., "NK1.1+ T cell receptor-alpha/beta+ cells: new clues to their origin, specificity, and function," <u>J. Exp. Med.</u> 182:633-638 (1995)
	Madsen, K.L., et al., "Interleukin 10 prevents cytokine-induced disruption of T84 barrier integrity and limits chloride secretion," <u>Gastroenterology</u> 113:151-159 (1997)
	Marth, T., et al., "High dose oral tolerance in ovalbumin TCR-transgenic mice: systemic neutralization of IL-12 augments TGF-beta secretion and T cell apoptosis," <u>J. Immunol.</u> 157:2348-2357 (1996)
	Matzinger, P., "Tolerance, danger, and the extended family," <u>Ann. Rev. Immunol.</u> 12:991-1045 (1994)
	Mizoguchi, A., et al., "Cytokine imbalance and autoantibody production in T cell receptor-alpha mutant mice with inflammatory bowel disease," <u>J. Exp. Med.</u> 183:847-856 (1996)
	Murch, S.H., et al., "Location of tumour necrosis factor alpha by immunohistochemistry in chronic inflammatory bowel disease," <u>Gut</u> 34:1705 (1998)
	Nakano, Y., et al., "Permanent acceptance of liver allografts by intraportal injection of donor spleen cells in rats," <u>Surgery</u> 111:668-676 (1992)
	Neurath, M.F., et al., "Antibodies to interleukin 12 abrogate established experimental colitis in mice," <u>J. Exp. Med.</u> 182:1281-1290 (1995)
	Neurath, M., et al., "Experimental granulomatous colitis in mice is abrogated by induction of TGF-beta-mediated oral tolerance," <u>J. Exp. Med.</u> 183:2605-2616 (1996)
	Onoe, Y., et al., "Involvement of both donor cytotoxic T lymphocytes and host NK1.1+ T cells in the thymic atrophy of mice suffering from acute graft-versus-host disease," <u>Immunology</u> 95:248-256 (1998)

EXAMINER

DATE CONSIDERED

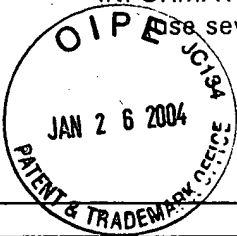
\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce

(REV. 8-83) Patent and Trademark Office

## INFORMATION DISCLOSURE CITATION

(See several sheets if necessary)

Atty. Docket No.  
ENZ-63(CIP)

Serial No. 10/676,045

Applicants: Ilan, et al

Filed: Sep. 30, 2003

Group: Not yet known

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Parronchi, P., et al., "Type 1 T-helper cell predominance and interleukin-12 expression in the gut of patients with Crohn's disease," <i>Am. J. Pathol.</i> 150:823-832 (1997)
	Podolsky, D.K., et al., "Inflammatory bowel disease," <i>New Engl. J. Med.</i> 325:928-935 (1991)
	Pouwels, P.H., et al., <i>Cloning Vectors, A Laboratory Manual</i> , Elsevier, New York (1985)
	Powrie, F., et al., "Inhibition of Th1 responses prevents inflammatory bowel disease in scid mice reconstituted with CD45RBhi CD4+ T cells," <i>Immunity</i> 1:553-562 (1994)
	Qin, S., et al., "'Infectious' Transplantation Tolerance," <i>Science</i> 259:974-977 (1993)
	Raedler, A., et al., "Elevated numbers of peripheral T cells in inflammatory bowel diseases displaying T9 antigen and Fc alpha receptors," <i>Clin. Exp. Immunol.</i> 60:518-526 (1985)
	Rodriguez, R.L., et al., <i>Vectors: A Survey of Molecular Cloning Vectors and their Uses</i> , Butterworth-Heinemann, Boston (1987)
	Sadlack, B., et al., "Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene," <i>Cell</i> 75:253-261 (1993)
	Sander, J.H., et al., "Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's Disease Study Group," <i>Gastroenterology</i> 113:383-89 (1997)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce

(REV. 8-83) Patent and Trademark Office

## INFORMATION DISCLOSURE CITATION

(use several sheets if necessary)

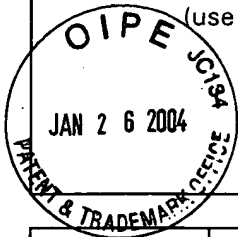
Atty. Docket No.  
ENZ-63(CIP)

Serial No. 10/676,045

Applicants: Ilan, et al

Filed: Sep. 30, 2003

Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

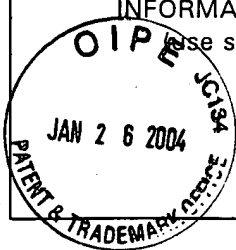
	Seder, R.A., et al., "Acquisition of Lymphokine-Producing Phenotype by CD4 + T Cells," <u>Annu. Rev. Immuno.</u> 12:635-673 (1994)
	Seder, R.A., et al., "Interleukin 12 Acts Directly on CD4 + T Cells to Enhance Priming for Interferon $\gamma$ Production and Diminishes Interleukin 4 Inhibition of Such Priming," <u>Proc. Natl. Acad. Sci. USA</u> 90:10188-10192 (1993)
	Seki, S., et al., "Unusual alpha beta-T cells expanded in autoimmune lpr mice are probably a counterpart of normal T cells in the liver," <u>J. Immunol.</u> 147:1214-1221 (1991)
	Sellon, R.K., et al., "Resident Enteric Bacteria are Necessary for Development of Spontaneous Colitis and Immune System Activation in Interleukin-10-Deficient Mice," <u>Infection and Immunity</u> 66:5224-5231 (1998)
	Strober, W., et al., "Reciprocal IFN-gamma and TGF-beta responses regulate the occurrence of mucosal inflammation," <u>Immunol. Today</u> 18:61-64 (1997)
	Strober, W., et al., <i>In Clinical Immunology</i> , Mosby, St. Louis, pp. 1401-1428 (1995)
	Takahashi, F., et al., "Isolation and characterization of a colonic autoantigen specifically recognized by colon tissue-bound immunoglobulin G from idiopathic ulcerative colitis," <u>J. Clin. Invest.</u> 76:311-318 (1985)
	Takahashi, M., et al., "LPS induces NK1.1 + alpha beta T cells with potent cytotoxicity in the liver of mice via production of IL-12 from Kupffer cells," <u>J. Immunol.</u> 156:2436-2442 (1996)
	Telemeo, E., et al., "Oral tolerance in experimental animals," <u>Int. Arch. Allergy Immunol.</u> 113:219-223 (1997)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office  INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

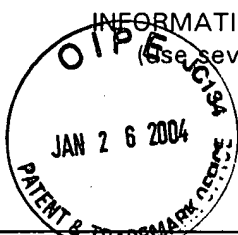
DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRANS- LATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Trop, S., et al., "Liver-Associated Lymphocytes Expressing NK1.1 Are Essential for Oral Immune Tolerance Induction in a Murine Model," <u>Hepatology</u> 29:746-755 (1999)
	Vicari, A.P., et al., "Mouse NK1.1 + T cells: a new family of T cells," <u>Immunology Today</u> 17(2):71 (1996)
	Von Herrath, M.G., et al., "Oral Insulin Treatment Suppresses Virus-induced Antigen-specific Destruction of $\beta$ Cells and Prevents Autoimmune Diabetes in Transgenic Mice," <u>J. Clin. Inves.</u> 98:1324-1331 (1996)
	Wahl, et al., "Improved radioimaging and tumor localization with monoclonal F(ab') <sub>2</sub> ," <u>J. Nucl. Med.</u> 24:316-325 (1983)
	Weiner, H., et al., "Oral Tolerance: Immunologic Mechanisms and Treatment of Animal and Human Organ-Specific Autoimmune Diseases by Oral Administration of Autoantigens," <u>Annu. Rev. Immunol.</u> 12:809-837 (1994)
	Weiner, H., et al., "Oral Tolerance," <u>Proc. Natl. Acad. Sci. USA</u> 91:10762-10765 (1994)
	Weiner, H.L., et al., "Oral tolerance: immune mechanisms and treatment of autoimmune diseases," <u>Immunol. Today</u> 18:335-343 (1997)
	Weiner, H.L., et al., "Double-blind pilot trial of oral tolerization with myelin antigens in multiple sclerosis," <u>Science</u> 259:1321-1324 (1993)
	Yoshimoto, T., et al., "CD4pos, NK1.1pos T cells promptly produce interleukin 4 in response to in vivo challenge with anti-CD3," <u>J. Exp. Med.</u> 179:1285-1295 (1994)

EXAMINER	DATE CONSIDERED
----------	-----------------

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office 	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

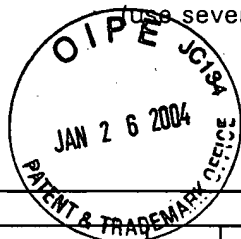
DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRANS- LATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Yoshimoto, T., et al., "Role of NK1.1+ T Cells in a TH2 Response and in Immunoglobulin E Production," <u>Science</u> 270:1845-1847 (1995)
	Yu, S.Y., et al., "Portal vein administration of donor cells promotes peripheral allospecific hyporesponsiveness and graft tolerance," <u>Surgery</u> 116:229-234 (1994)
	Burdin, N., et al., "Immunization with alpha-galactosylceramide polarizes CD1-reactive NKT cells towards Th2 cytokine synthesis," <u>Eur J. Immunol.</u> 29:2014-2025 (1999)
	Gotsman, I., et al., "Effect of peripheral immune tolerance on liver-associated lymphocytes expressing NK1.1," <u>Transplant Proc.</u> 32:749-750 (2000)
	Shlomai, A., et al., "Immunomodulation of experimental colitis: the role of NK1.1 liver lymphocytes and surrogate antigens - bystander effect," <u>J. Pathology</u> 195:498-507 (2001)
	Sredni, B., et al., "Predominance of TH1 response in tumor-bearing mice and cancer patients treated with AS101," <u>J. Natl. Cancer Inst.</u> 88:1276-1284 (1996)
	Angulo, P., "Nonalcoholic fatty liver disease," <u>New England J. of Medicine</u> 346:1221-1231 (2002)
	Caldwell, S.H., et al., "Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease," <u>Hepatology</u> 29:664-669 (1999)
	Chandra, R.K., et al., "Immunocompetence in obesity," <u>Acta Paediatr. Scand.</u> 69:25-30 (1980)
	Cohen, B., et al., "Modulation of Insulin Activities by Leptin," <u>Science</u> 274:1185 (1996)

EXAMINER	DATE CONSIDERED
*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office  INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

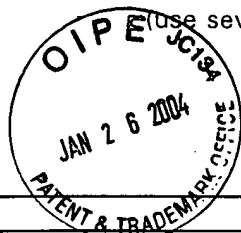
	Cortez-Pinto, H., et al., "Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study," <u>JAMA</u> 282:1659-1664 (1999)
	Diehl, A.M., et al., "Nonalcoholic Steatosis and Steatohepatitis IV. Nonalcoholic fatty liver disease abnormalities in macrophage function and cytokines," <u>J. Physiol. Gastrointest. Liver Physiol</u> 282:G1-G5 (2002)
	Faggioni, R., et al., "Leptin-deficient ( <i>ob/ob</i> ) mice are protected from T cell-mediated hepatotoxicity: Role of tumor necrosis factor $\alpha$ and IL-18," <u>Proc. Natl. Acad. Sci. USA</u> 97:2367-2372 (2000)
	Feingold, C.T., et al., "Role of cytokines in inducing hyperlipidemia," <u>Diabetes</u> 41(Suppl 2):97-101 (1992)
	Ferrara, J.L.M., et al., "Graft-versus-host disease," <u>New Eng. J. of Med.</u> 324:667-672 (1991)
	Field, C.J., et al., "Changes in circulating leukocytes and mitogen responses during very-low- energy all-protein reducing diets," <u>Am. J. Clin. Nutr.</u> 54:123-129 (1991)
	George, D.K., et al., "Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis," <u>Gastroenterology</u> 114:311-318 (1998)
	Godfrey, D.J., et al., "NKT cells: Facts, functions and fallacies," <u>Immunol. Today</u> 21:573-583 (2000)
	Harrison, S.A., et al., "Vitamin E and Vitamin C in the Treatment of Nonalcoholic Steatohepatitis. A Prospective, Randomized, Placebo-Controlled Clinical Trial. A Preliminary Report," <u>Gastroenterology</u> 123:M1332 (2002)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office  INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

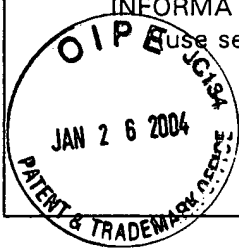
	Hotamisligil, G.S., et al., "Adipose expression of tumor necrosis factor-[alpha]: direct role in obesity-linked insulin resistance," <u>Science</u> 259:87-91 (1993)
	Hotamisligil, G.S., "The role of TNFalpha and TNF receptors in obesity and insulin resistance," <u>J. Internal Med.</u> 245:621-625 (1999)
	Howard, J.K., et al., "Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in <i>ob/ob</i> mice," <u>J. Clin. Invest.</u> 104:1051-1059 (1999)
	Hruszkewycz, A.M., et al., "Evidence for mitochondrial DNA damage by lipid peroxidation," <u>Biochem. Biophys. Res. Commun.</u> 153:191-197 (1988)
	Koffler, M., et al., "Immunobiological consequence of regulation of insulin receptor on alloactivated lymphocytes in normal and obese subjects," <u>Diabetes</u> 40:364-370 (1991)
	Krishnan, E., et al., "Study of function and maturation of monocytes in morbidly obese individuals," <u>J. Surg. Res.</u> 33:89-97 (1982)
	Li, Z., et al., "Murine leptin deficiency alters Kupffer cell production of cytokines that regulate the innate immune system," <u>Gastroenterology</u> 123:1304-1310 (2002)
	Loffreda, S., et al., "Leptin regulates proinflammatory immune responses," <u>FASEB J</u> 12:57-67 (1998)
	Lord, G.M., et al., "Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression," <u>Nature</u> 394:897-901 (1998)
	Mattacks, C.A., et al., "Interactions of noradrenalin and tumour necrosis factor alpha, interleukin 4 and interleukin 6 in the control of lipolysis from adipocytes around lymph nodes," <u>Cytokine</u> 11:334-346 (1999)
	Matteoni, C.A., et al., "Nonalcoholic Fatty Liver Disease: A Spectrum of Clinical and Pathological Severity," <u>Gastroenterology</u> 116:1413 (1999)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office  INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

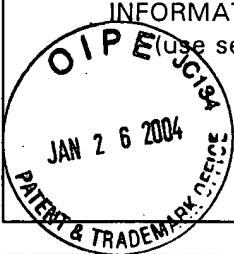
	Mitchell, D.G., et al., "Chemical shift phase-difference and suppression magnetic resonance imaging techniques in animals, phantoms and humans: fatty liver," <u>Invest. Radiol.</u> 26:1041-1052 (1991)
	Montague, C.T., et al., "Depot-related gene expression in human subcutaneous and omental adipocytes," <u>Diabetes</u> 47:1384-1391 (1998)
	Nagler, A., et al., "Induction of oral tolerance in bone marrow transplantation recipients suppresses graft-versus-host disease in a semiallogeneic mouse model," <u>Bone Marrow Transplantation</u> 32:363-369 (2003)
	Ogawa, H., et al., "Cachectin/tumor necrosis factor and interleukin-1 show different modes of combined effect on lipoprotein lipase activity and intracellular lipolysis in 3T3-L1 cells," <u>Biochimica et Biophysica Acta</u> 1003:131-135 (1989)
	Pellymounter, M.A., et al., "Effects of the obese gene product on body weight regulation in ob/ob mice," <u>Science</u> 269:540-543 (1995)
	Pond, C.M., et al., "Long-term changes in adipose tissue in human disease," <u>Proc. Nutr. Soc.</u> 60:365-374 (2001)
	Purohit, A., et al., "Aromatase activity and interleukin-6 production by normal and malignant breast tissues," <u>J. Clin. Endocr. &amp; Metab.</u> 80:3052-3058 (1995)
	Rosen, B.S., et al., "Adipsin and complement factor D activity: an immune-related defect in obesity," <u>Science</u> 244:1483-1487 (1989)
	Sanyal, A.J., et al., "Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities," <u>Gastroenterology</u> 120:1183-1192 (2001)
	Sarraf, P., et al., "Multiple Cytokines and Acute Inflammation Raise Mouse Leptin Levels: Potential Role in Inflammatory Anorexia," <u>J. Exp. Med.</u> 185:171-175 (1997)

EXAMINER

DATE CONSIDERED

\*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce (REV. 8-83) Patent and Trademark Office  INFORMATION DISCLOSURE CITATION (use several sheets if necessary)	Atty. Docket No. ENZ-63(CIP)	Serial No. 10/676,045
	Applicants: Ilan, et al	
	Filed: Sep. 30, 2003	Group: Not yet known



## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPRO- PRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	TRAN- SLATION YES NO

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

	Shilobet, O., et al., "NKT and CD8 lymphocytes mediate suppression of hepatocellular carcinoma growth via tumor antigen-pulsed dendritic cells," <u>Int. J. Cancer</u> 106:236-243 (2003)
	Taylor, P.A., et al., "The infusion of ex vivo activated and expanded CD4 <sup>+</sup> CD25 <sup>+</sup> immune regulatory cells inhibits graft-versus-host disease lethality," <u>Blood</u> 99:3493-3499 (2002)
	Tomohiro, N., et al., "Aromatase activity and interleukin-6 production by normal and malignant breast tissues," <u>Radiology</u> 218:642-646 (2001)
	Trop, S., et al., "NK 1.1 + T Cell: A Two-Faced Lymphocyte in Immune Modulation of the IL-4/IFN- Paradigm," <u>J. Clin. Immunol.</u> 22:270-280 (2002)
	Uysal, K.T., et al., "Protection from obesity-induced insulin resistance in mice lacking Tnf-alpha function," <u>Nature</u> 389:610-614 (1997)
	Vogelsang, G.B., et al., "Graft versus host disease: Implications from basic immunology for prophylaxis and treatment," <u>Cancer Treat. Res.</u> 77:87-97 (1997)
	Yang, et al., "Obesity increases sensitivity to endotoxin liver injury: Implications for the pathogenesis of steatohepatitis," <u>Proc. Natl. Acad. Sci USA</u> 94:2557-2562 (1997)
	Zeng, D., et al., "Bone Marrow NK1.1 <sup>-</sup> and NK1.1 <sup>+</sup> T Cells Reciprocally Regulate Acute Graft versus Host Disease," <u>J. Exp. Med.</u> 189:1073-1081 (1999)
	Zhang, Y., et al., "Positional cloning of the mouse obese gene and its human homologue," <u>Nature</u> 372:425-432 (1994)

EXAMINER	DATE CONSIDERED
*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	